Deciphering Phosphodiesterase-5 Inhibitors from Aframemum melegueta: Computational Models against Erectile dysfunction

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Abstract

Insufficient and inability to maintain erection in male for satisfactory sexual performance remains global challenge among couples. The identification of phosphodiesterase-5 (PDE-5) antagonist in the pathogenesis of erectile dysfunction has improved the search for therapeutic agents for the management of this sexual dysfunction. Here in, bioactive compounds from *Aframomum melegueta* were virtually screened against PDE-5 using Schrodinger suite 2017-1 as computational tool. The lead compound was further validated in comparison with Viagra by performing 100 ns molecular dynamics (MD) simulation using Desmond. Among 109 bioactive compounds screened, nine (9) molecules were predicted as potent inhibitors of PDE-5 with binding affinities comparable to the co-crystalized ligand (sildenafil). 1,7-bis(3,4-dihyroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate was observed to have the best docking score (-11.522 kcal/mol) among the hit compounds which is very close to the co-crystalized ligand (-11.872 kcal/mol). Validation using pharmacophore hypothesis and QSAR modeling further confirmed the prediction of the hit compounds with fitness score ranging from 0.754 to 2.605 and predicted pIC50 of 3.835 to 7.976 μM. All the hit compounds obeyed Lipinski's rule of five and within the reference range of the pharmacokinetics parameters. The MD simulation result predicted the stability of 1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate-PDE-5 complex comparable to the sildenafil-PDE-5 complex. The outcome of this study predicted nine molecules from *A. melegueta* as potent PDE-5 antagonists which required isolation and experimental validation for the management of erectile dysfunction.

Introduction

Sexual dysfunction in male is defined as failure to accomplish sexual relationship satisfactorily (Valerie et al., 2020). This condition might result from erectile dysfunction, early ejaculation, reduced sexual desire, ageing, sedentary life style, diminished libido among others. Erectile dysfunction refers to insufficient penile erection required for satisfactory sexual intercourse (Palanichamy et al., 2022). The recurrent penile erection dysfunction for accomplishing sexual performance is also known as impotence (Valerie et al., 2020). WHO (2000), reported that male sexual ability was observed to be deficient in about 50% of infertile couples which remains the major factor that decrease the probability of conception in the spouse (Kamtchouinga et al., 2002). This male poor sexual performance is the leading cause of infidelity among married women globally.

Penile erection is under autonomic nervous control resulting from hemodynamic events such as erotic stimulus (Allas et al., 1999). This event stimulates the release of nitric oxide from vascular endothelium, followed by activation of guanylyl cyclase which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cCMP). This second messenger activates K^+-channel, resulting into hyperpolarization of the penile smooth muscle with reduced intracellular Ca^{2+}. This eventually relaxes the smooth muscle of the penis and increases the rate of blood flow leading to penile erection (Francis et al., 2010). High concentration of phosphodiesterase-5 (PDE-5) in the penile arterial smooth muscle reduces the availability of cGMP by converting it to 5'-GMP therefore terminating penile smooth muscle

relaxation and end erectile process (Francis et al., 2010). This phosphodiesterase enzyme is an important therapeutic target for erectile dysfunction and most drugs such as sildenafil and natural herbs act by inhibiting the activity of PDE-5 (Fig. 1) to restore penile erection making it last long (Kenia, 2012).

Although synthetic drugs such as Viagra have yielded therapeutic achievement in erectile management, but the present of unwanted side effects such as penile pain, dyspepsia, dizziness and risk of prostate cancer associated to these aphrodisiacs has necessitated search for natural herbs with erectogenic ability and reduced or no side effects (Ajay, 2007). *Aframomum melegueta* popularly known as alligator pepper is a member of Zingiberaceace family. Ataare has the plant is popularly called among the Yoruba tribe of Nigeria is a spice that is use traditionally for entertainment, food flavor and herbal medication (Omoboyowa et al., 2017). Although the plant seed has been exploited for its erectogenic potential (Adefegha et al., 2017; Okeke et al., 2018; Nguimatio et al., 2019), the mechanism of erectogenic potential of the bioactive compounds from alligator pepper has not been studied. Hence this study is aimed at predicting highly effective compounds from *A. melegueta* for achieving penile erection and delay ejaculation in other to improve male sexual performance. To achieve this goal, molecular docking, pharmacophore hypothesis, QSAR modeling and molecular dynamics simulation of the bioactive molecules from *A. melegueta* was performed against PDE-5. Further pharmacokinetics and drug likeness profile of the hit compounds were studied to predict the safety of these compounds as drug candidates.

Materials and Methods

Generation and Preparation of Compound library

Google search and pubchem database were used to access previously published articles on isolation, characterization and identification of bioactive compounds from *Aframomum melegueta* leaves, seeds and stem bark. The 3-dimensional structures of one hundred and nine (109) bioactive compounds from *A. melegueta* were retrieved via pubchem.ncbi.nlm.nih.gov alongside with a standard drug (sildenafil) in structure data file (sdf) format. These molecules were exported onto Schrodinger workspace (Schrodinger, 2017) and prepared using Ligprep tool for the *in silico* study.

Protein Preparation

The research collaborator for structural bioinformatics protein databank (RCSB PDB) [www.rcsb.org] website provided the x-ray crystallographic structure of human phosphodiesterase-5 complex with sildenafil (Viagra) having PDB ID of 1UDT and 2.3 Å resolution (RCSB). The missing residues and loop in the protein and other side chain anomalies were resolved, followed by energetic optimization with force field OPLS3 using protein preparation wizard of Schrodinger suit 2017-1. The receptor grid generator was used to generate glide grid on the co-ligand (sildenafil) attached site with glide coordinate of x = 1.6; y = 67.23 and z = 83.39. The prepared protein crystallographic structure and Ramachadran residues' distribution are shown in Fig. 2.

Validation and Structure-based virtual screening

Molecular docking analysis is a virtual screening procedure involve in drug design to predict binding affinity of bioactive molecules against protein targets (Bodun et al., 2023). Prior to the molecular screening, the co-crystalized ligand (sildenafil) was extracted from the binding domain of the target and docked to the same binding site of 1UDT to predict the molecular interaction and RMSD (root mean square deviation) of the co-crystalized ligand and re-docked ligand for validation of the docking protocol (Omoboyowa et al., 2023).

Three filtering procedures were used to screen the 109 molecules from *A. melegueta* against PDE-5. The high throughput virtual screen (HVTS) precision method was first used. Top scored 18.35% ((Omoboyowa, 2022b) molecules were further screened against the target using the standard precision (SP) docking method. Ten (10) top scored compounds were further screened with extra precision (XP) method (Omoboyowa, 2022). Complexes with binding affinity above 8.00 Kcal/mol were reported as potent inhibitors of PDE-5 and subjected to further validation.

Although the XP precision docking protocol showed the interaction and conformation of the complexes, the free binding energy of the complexes was carried out to further validate the biological activity and stability using prime module of maestro Schrodinger Omoboyowa et al., 2022). The binding energy was estimated based on the formula:

$$\Delta G^{bind} = G^{complex} \times -(G^{protein} + G^{Ligand})$$

Virtual Screening of Hits using E-pharmacophore Hypothesis

Energy-optimized pharmacophore hypothesis was generated for the phosphodiesterase-5 (1UDT) x-ray crystallographic structure complex with sildenafil as co-crystalized ligand by pharmacophore protein-ligand Complex using the Phase modules option. Four features with molecular interactions with the target were selected for setting the pharmacophore hypothesis. Receptor binding site was mimic by the generated receptor-based excluded volume shell, with the atoms whose surface were 2.00 Å within the ligand surface excepted and limiting excluded volume shell thickness to 5.00 Å (Bodun et al., 2023). The preparation of the nine compounds alongside sildenafil was performed with macromodel minimization and screened via the E-pharmacophore hypothesis generated in Schrodinger suite (2017-1) using phase screen module. The hit compounds were evaluated for their fitness scores from the hypothesis.

Virtual Screening of Hits using AutoQSAR Model

The FASTA sequence for phosphodiesterase-5 (1UDT) was downloaded from research collaborator for structural bioinformatics protein databank (RCSB PDB) [www.rcsb.org]. The experimental inhibitory datasets was downloaded from www.ebi.ac.uk/chembl. The reported inhibitory compounds against

phosphodiesterase-5 were downloaded with their respective pIC50, saved as sdf format using Data-warrior (v2) (Omoboyowa et al., 2023). The SDF file was prepared with macromodel minimization tool of Schrödinger suite (2017-1). Experimental pIC50 of the dataset was used to generate the autoQSAR model of the phosphodiesterase-5 (Dixon et al., 2016). The predicted top ranked model was chosen to predict the pIC50 of the hit molecules and sildenafil.

Drug-likeness and Pharmacokinetic prediction of Hit Compounds

The pharmacokinetic properties and drug-likeness prediction of the hit compounds were performed using QIKPROP tool of Schrodinger suite (2017-1).

Molecular dynamics (MD) simulation

MD simulation deals with the computation of atoms' movement per time by using classical motion of Newton. The stability of protein-ligand complex can be validated through MD simulation analysis. Based on the post-docking analysis of the extra precision virtual screening result, the MD simulation of the top scored ligand and reference ligand complex with phosphodiesterase-5 were performed for period of 100 ns using Desmond in Maestro Schrodinger. The simulation model was performed using the explicit solvent system, exploring TIP4P and orthorhombic box for the model preparation. Addition of sodium and chloride ions at 300◦k and 1.01325 bar neutralized the model. The simulation was run for 100 ns interval with OPLS-2005 force field (Omoboyowa et al., 2023). The trajectory generated was analyzed for RMSD, RMSF and contact summary using simulation interaction module of Desmond.

Results and discussion

Virtual screening of small molecules against protein targets is an important aspect of drug development, it predict the binding orientation of molecules to the active site of the target. To ascertain the reliability and reproducibility of the docking procedure, the co-crystalized ligand was extracted from the binding site and re-docked back into the binding domain. Figure 3 revealed the superimposition of the re-docked ligand with slight deviation from the original geometry with root mean square deviation (RMSD) of 1.423 Å, which was observed to be less than acceptable 2.00 Å (Omoboyowa et al., 2022b).

Post-docking analysis and binding free energy estimation

Molecular docking is a computational approach that predicts the interaction between receptor-ligand complexes through binding orientation of the ligands in the active site of the protein and ranking score of the interactions (Balogun et al., 2021). To predict potent inhibitors of PDE-5 for the management of erectile dysfunction, small molecules from *Aframomum melegueta* were screened against the binding site of PDE-5 with the binding affinity estimated using three glide filtering procedures. The binding affinity obtained from the extra precision (XP) mode is presented in Fig. 4. The nine (9) top scored compounds showed scores between − 11.522 kcal/mol to -8.152 kcal/mol compared with the binding affinity of the

co-crystalized ligand (sildenafil = -11.872 kcal/mol). Among the hit compounds, 1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate have the best binding affinity of -11.522 kcal/mol which is very close to the co-crystalized ligand. The binding affinity of sildenafil obtained in this study agrees with the value reported by Iwaloye et al. (Iwaloye et al., 2020); Khalid et al. (2022) also showed high binding affinity of sildenafil-PDE-5 complex (-10.01 kcal/mol) using autodock vina.

Table 1
Hydrogen bond interaction of Hits with Phosphodiesterase-5

Compounds	Compound Name	No of H-bond	Interacting residues
Co-ligand	Sildenafil	2	GLN 817 (1.82 Å); GLN 817 (4.98 Å)
CMPD 1	1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate	3	ASP 724 (2.38 Å); SER 663 (1.69 Å); SER 663 (2.02 Å)
CMPD 2	1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate	3	GLN 817 (5.24 Å); GLN 817 (2.49 Å); ASN 662 (2.00 Å)
CMPD 3	Apigenin	1	SER 663 (1.74 Å)
CMPD 4	quercetin-3,7,3,4_-tetramethylether	1	TYR 612 (2.29 Å)
CMPD 5	letestuianin A	2	GLN 775 (2.13 Å); ASP 724 (1.74 Å)
CMPD 6	kaempferol-3,7,4-trimethylether	Nil	Nil
CMPD 7	Buplerol	2	SER 663 (2.16 Å); GLN 817 (2.82 Å)
CMPD 8	letestuianin C	3	GLN 817 (2.00 Å); LEU 725 (2.65 Å); GLU 682 (2.27 Å)
CMPD 9	5-hydroxy-7-methoxyflavone	3	ASP 764 (3.39 Å); TYR 612 (2.04 Å); TYR 612 (2.74 Å)

E-Pharmacophore Hypothesis and fitness score of hit compounds

Generation of pharmacophore modeling based on small molecules formed an integral component of computational drug development. The hypothesis reports important features that are necessary for the inhibitory activity of active compounds (Miler and Roitberg, 2013). In this study, the ensemble of steric and electronic characters for phosphodiesterase-5 complex with sildenafil was generated using four

partitioning features for the identification of the hypothesis model. The hypothesis of the target with sildenafil is shown in Fig. 6. One hydrogen bond acceptor, two hydrogen bond donors, hydrophobic interaction and one aromatic ring were the features selected for the prediction of model with best fitness score. The screening of the hit compounds form *A. melegueta* was performed according to these features. The fitness scores of the nine (8) hit compounds and sildenafil are presented in Table 2. The co-crystalized ligand was observed to have the highest fitness score (2.605) compared with the hit compounds. Among the hit compounds, 5-hydroxy-7-methoxyflavone possesses the best fitness score of 1.986 while other compounds showed fitness score of less than 1.000 except 1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate with fitness score of 0.754. Fitness score is the quantitative measure of the fitness of ligand into the target with the considering the ligand interaction energies (Natarajan et al., 2015). Therefore, the sildenafil, 5-hydroxy-7-methoxyflavone, Apigenin and quercetin-3,7,3,4-tetramethylether might be predicted to fit well into the binding site of PDE-5 than other bioactive compounds. All the bioactive molecules showed positive fitness score, these showed that they fit into the target.

Table 2
Hit compounds fitness score via pharmacophore model

Compound Label	Compound Name	Fitness Score
Co-ligand	Sildenafil	2.605
CMPD 1	1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate	1.187
CMPD 2	1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate	0.754
CMPD 3	Apigenin	1.908
CMPD 4	quercetin-3,7,3,4-tetramethylether	1.904
CMPD 5	letestuianin A	1.483
CMPD 6	kaempferol-3,7,4-trimethylether	1.355
CMPD 7	Buplerol	1.247
CMPD 8	letestuianin C	1.312
CMPD 9	5-hydroxy-7-methoxyflavone	1.986

AutoQSAR modeling and pIC50 Prediction of hit compounds

Quantitative structure-activity relationship (QSAR) is an automated machine learning tool for validating, building and deploying structural-activity relationship models (Dixion et al., 2016). AutoQSAR is a computational tool that reveals the relationship between the biological potency and structures of small

molecules which is crucial in computational drug development (Kwon et al., 2019). In this study, kpls_desc_6 was selected as the best partial least square regression (kpls) analysis predicted from the QSAR model. The kpls was categorized into 25% test and 75% train set (table S1). The predicted activity against observed activity plot is revealed in Fig. 7, it was observed that more train set (blue colour) were present on the plot compared with test set (red colour) which correlate strongly with table S1. The analysis of the selected model parameters showed the standard deviation (SD) as 0.5804, R^2 as 0.8833, RMSE as 0.7401and Q^2 as 0.7737 as shown in Table 3. The generated autoQSAR model was use to predict the pIC50 of the hit molecules and presented in Table 4, all the hit ligands and sildenafil were observed to have high pIC50 more than 5.00 µM except 1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate (pIC50 = 3.835). The co-crystalized ligand (7.976 µM) showed the highest pIC50 than the hit compounds. The value of negative logarithm of IC50 is pIC50 and is necessary to compare the potency of small molecules at the same molar levels. High values of pIC50 indicate exponentially more potent inhibitors (Stewart and Watson, 1983). Hence, the hit compounds and sildenafil were suggested as potent inhibitor of phosphodiesterase-5.

Table 3
Parameters of the predicted model

Model code	S.D	R^2	RMSE	Q^2
kpls_desc_6	0.5804	0.8833	0.7401	0.7737

Table 4
Predicted pIC50 for the hit molecules via QSAR model

Compound Label	Compound Name	Predicted pIC50 (μM)
Co-ligand	Sildenafil	7.976
CMPD 1	1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate	5.592
CMPD 2	1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate	3.835
CMPD 3	Apigenin	4.765
CMPD 4	Quercetin-3,7,3,4_-tetramethylether	6.536
CMPD 5	Letestuianin A	6.167
CMPD 6	Kaempferol-3,7,4-trimethylether	5.742
CMPD 7	Buplerol	5.706
CMPD 8	Letestuianin C	5.727
CMPD 9	5-hydroxy-7-methoxyflavone	5.459

Pharmacokinetic and drug-likeness evaluation of small molecules as drug candidates is vital in their prediction as novel therapeutic agents. Hence, high percentage of potential drugs failed the stage of clinical trial as a result of poor pharmacokinetic profile with high toxicity rate (Omoboyowa et al., 2021). Due to the time consuming and cost of in vivo toxicity study, *in silico* model of pharmacokinetic screening remains the fastest and cost-effective approach. In this study, selected pharmacokinetic profiles such as IC50 value for the blockage of HERG K (QPLog^{HERG}), apparent calcium carbonate (QPCaco), madin-Darby canine kidney (MDCK) cell, brain/blood partition coefficient (QPlogBB) and percentage oral absorption were predicted using the Qikprop tool of Schrodinger suite.

The physicochemical profile of the hit compounds presented in Table 5 revealed that, compound 2 [1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate] exhibit poor Caco cell permeability value below 25 nm/s, blood brain partition coefficient below − 3.0, MDCK value and percentage oral absorption. The Caco cell lines remain a model for human intestinal absorption prediction of drug candidates (Van-Breemen and Li, 2005). This blood-brain partition coefficient is vital in the prediction of drug molecules that can penetrate the central nervous system and MDCK cells are utilized in investigating the rate of drug efflux during drug design (Omoboyowa, 2022b). The QPLog^{HERG} value for the co-crystalized ligand and letestuianin A (-6.33 and − 6.31 respectively) were observed to deviate from the reference range while all other molecules were predicted with pharmacokinetic indices within the reference range with high percentage oral absorption.

The result of the predicted drugability of the hit molecules was represented in Table 6, except 1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate which violated one Lipinski's rule of five, The hit molecules obeys all the Lipinski's rule of five with molecular weight less than 50Da, number of hydrogen bond donor less than 5 but compound 2 has 6, number of hydrogen bond acceptor less than 10 (Lipinski et al., 2001), but the co-crystalized ligand has 11.75. Compounds 1 and 2 were observed to exhibit a high topological surface area of 169.85 and 190.70 respectively.

Table 5
Pharmacokinetic prediction of Hit molecules

Entry Name	$QPlog^{HERG}$	QPP^{Caco}	$QPlog^{BB}$	QPP^{MDCK}	% ORAL ABS
Co-Ligand	-6.33	129.73	-0.96	60.19	77.47
Compound 1	-5.08	48.95	-2.90	18.97	74.61
Compound 2	-1.58	0.21	-4.13	0.08	17.04
Compound 3	-5.12	116.16	-1.44	48.28	73.34
Compound 4	-5.05	504.86	-0.74	236.33	87.86
Compound 5	-6.31	284.41	-1.82	127.09	93.91
Compound 6	-4.95	9906.04	-0.38	5899.29	100.00
Compound 7	-4.57	889.32	-0.91	435.80	100.00
Compound 8	-5.83	201.91	-1.81	87.76	83.64
Compound 9	-5.28	1235.16	-0.41	621.57	100.00
Reference values: $Qplog^{HERG}$ = below − 5; $QPlog^{BB}$ = -3.0 to 1.2; QPP^{Caco} = < 25 poor, > 500 great					

Table 6
Drug likeness prediction of hit molecules

Entry Name	MW	HBD	HBA	TPSA	RO5
Co-Ligand	474.58	1.00	11.75	119.09	0
Compound 1	492.52	4.00	8.50	169.85	0
Compound 2	462.50	6.00	7.75	190.70	1
Compound 3	270.24	2.00	3.75	100.03	0
Compound 4	296.28	0.00	4.75	89.04	0
Compound 5	324.38	2.00	3.25	87.36	0
Compound 6	324.38	0.00	2.75	28.35	0
Compound 7	372.42	1.00	6.00	85.35	0
Compound 8	312.37	2.00	5.50	95.15	0
Compound 9	268.27	0.00	3.00	63.25	0

Molecular weight (MW), Hydrogen bond donor (HBD), Hydrogen bond acceptor (HBA), topological surface area (TPSA), Rule of five (RO5)

Result of the MD simulation

The result of docking and post-docking study the bioactive compounds from *Aframemum melegueta* against phosphodiesterase-5 revealed nine (9) compounds as potential inhibitor of the target. From these compounds, 1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate possess the highest binding affinity compared with the standard ligand. Therefore, conformational stability of 1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate and sildenafil complex with PDE-5 were validated using 100 ns MD simulation.

Root-mean-square-deviation Analysis

The analysis of the stability of docked complex is a vital index for predicting the mechanism of inhibition of ligand-protein complex during virtual screening. The root-mean-square-deviation (RMSD) gives detail concerning the structural backbone of the target protein (Omboyowa et al., 2023). From Fig. 8, the RMSD plot of the target (Cα) and ligands fit protein over 100 ns MD trajectory revealed initial deviation of less than 1.2 Å of the compound-protein complex over 20 ns between the protein and the ligand with stability observed from 20–100 ns of simulation time. The stability observed in the active complex simulation was similar to the observed stability in the co-ligand-protein complex, although there was no initial deviation in the co-ligand-protein complex but minimal fluctuation of less than 2.0 Å. The deviation that was observed in the active compound-protein complex was acceptable for small globular protein. The

stability observed in the RMSD plot of the compound and co-ligand-protein complex is consistent with the close binding affinity observed in the molecular docking and post-docking analysis.

Result of Root-mean-square-fluctuation (RMSF)

The computation of the atomic fluctuation of the position of residues of protein backbone is use to evaluate the dynamic behavior protein–ligand complexes. The positional changes in the amino acid of phosphodiesterase-5 were analyzed using root-mean-square-fluctuation within 100 ns of simulation. Figure 9 shows that, the β-strands and α-helices of the protein crystal structure was observed to oscillate between 0.6–5.4 Å for the lead compound and 0.5–3.5 Å for the co-crystalized ligand (sildenafil). There was less fluctuation in the target's secondary parameters (β-strands and α-helices) due to their stability compared with the unstructured part of the target. There was high level of fluctuation at the loop region of the protein up to 5.4 Å for the co-ligand but 3.5 Å for the lead compounds.

Protein-Ligand complex interaction mapping

The docking orientation of phosphodiesterase-5-ligand complex was validated for intermolecular contact using the complex contact mapping from individual frame of the trajectory for 100 ns simulation time as shown in Fig. 10. The co-crystalized ligand and compound 1 interacted with the amino acid residue at the binding site of phosphodiesterase-5 with hydrogen bond, hydrophobic bond and water bridges. Glutamine 817 (GLN 817) was observed in both complexes to possess higher interaction fraction of hydrogen bond. Compound-1-PDE-5 complex was predicted to possess more hydrogen bond which might contribute to the stability of the complex than the co-crystalized-PDE-5 complex.

Conclusion

Phosphodiesterase type 5 (PDE-5) has been predicted as drug target for erectile dysfunction. Therefore, this study has predicted the antagonistic potency of nine (9) out of one hundred and nine (109) bioactive compounds from *A. melegueta* as potential inhibitors of PDE-5 using computational approach. The report of the binding affinity of the hit molecules against the target was further validated with pharmacophore hypothesis and QSAR model. The result showed favorable binding interaction via the fitness scores and predicted pIC50 values for the nine hit compounds. All the lead compounds also revealed acceptable pharmacokinetic status and obey Lipinski's rule of five with maximum of one violation, predicting the hit compounds as drug candidates. The molecular dynamic simulation result that 1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate-PDE-5 complex is very stable comparable to the sildenafil-PDE-5 complex. This compound is therefore suggested for isolation from the plant and further experimental evaluation for the development of therapeutic agents for erectile dysfunction in male.

Declarations

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Conflict of interest

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Statement of authorship

Omoboyowa Damilola Alex: Conceptualization, Investigation, Methodology, Analysis, Resources, Writing - Original Draft, Review & Editing.

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Figures

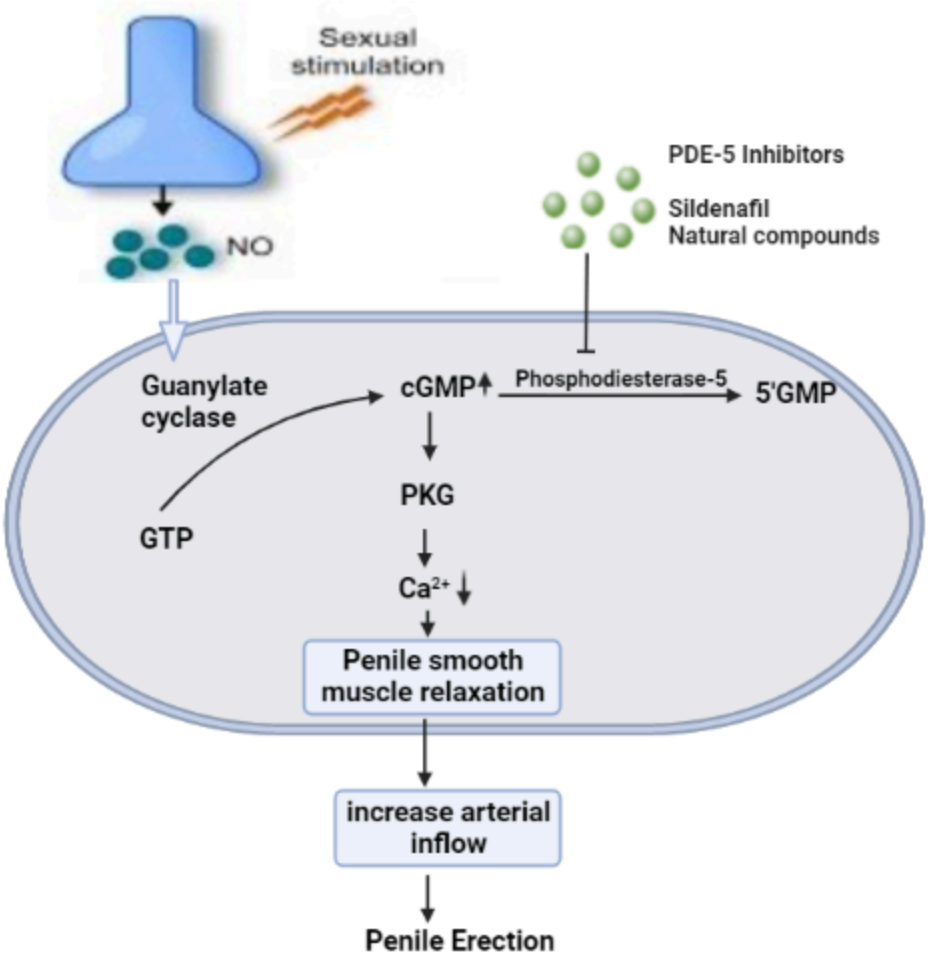


Figure 1

Signaling mechanism of erectile process with PDE-5 inhibitors

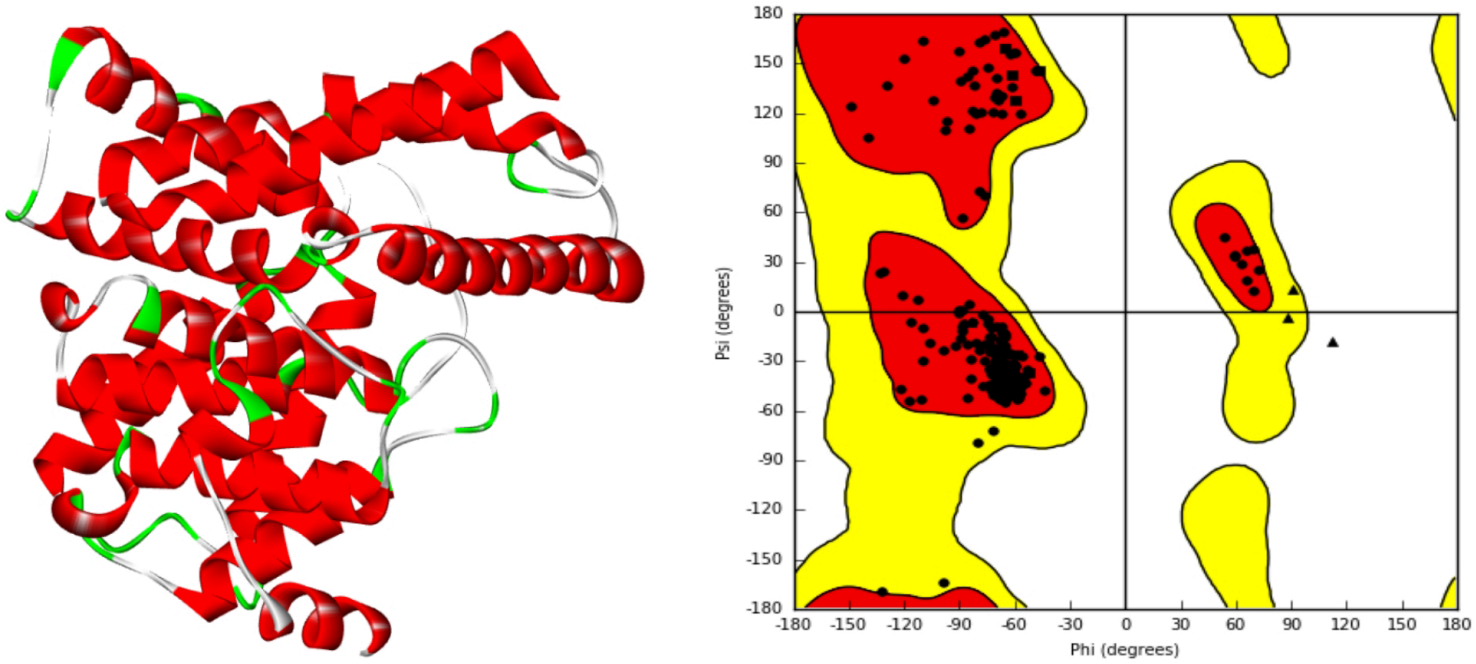


Figure 2

Crystal structure of PDE-5 and Ramachandran plot of residues distribution

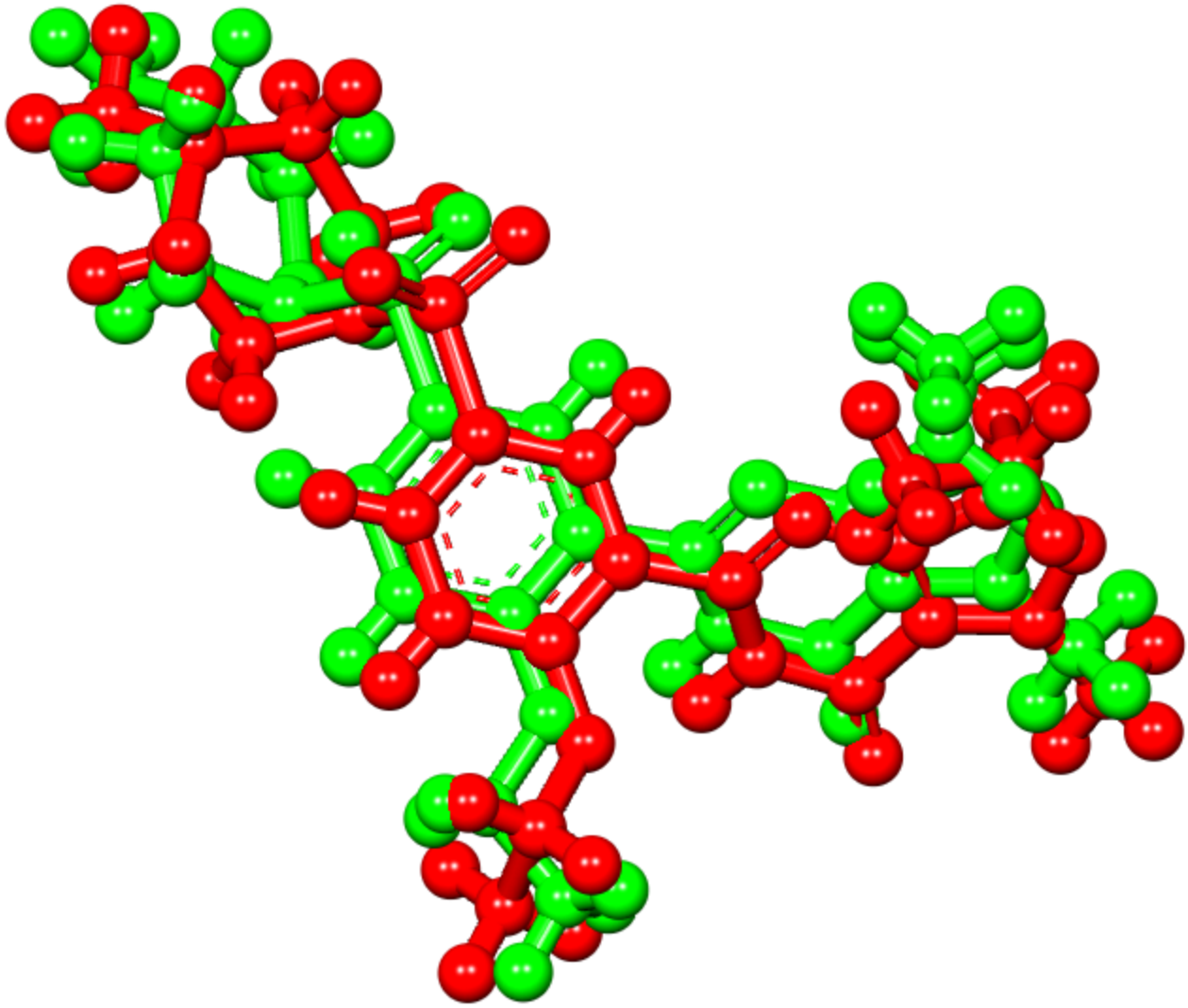


Figure 3

Superimposition of sildenafil at the active site of PDE-5

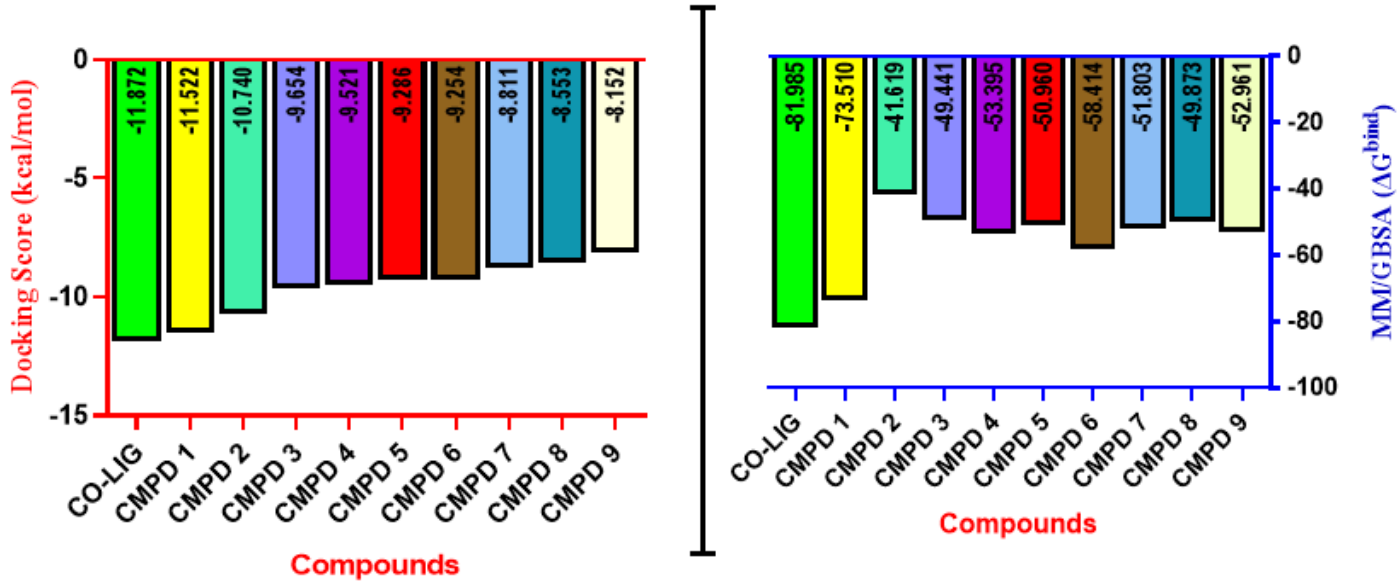


Figure 4

Binding affinity and Binding Energies of the hit compounds from *A. melegueta* against PDE-5

viz: Co-ligand – Sildenafil; CMPD 1- 1,7-bis(3,4-dihydroxy-5-methoxyphenyl)heptane-3,5-diyldiacetate; CMPD 2 - 1-(3,4-dihydroxy-5-methoxyphenyl)-7-(3,4-dihdroxyphenyl)heptane-3,5-diyldiacetate; CMPD 3- Apigenin; CMPD 4 - quercetin-3,7,3,4_-tetramethylether; CMPD 5 - Letestuianin A; CMPD 6 - kaempferol-3,7,4-trimethylether; CMPD 7- Buplerol; CMPD 8 - Letestuianin C; CMPD 9 - 5-hydroxy-7-methoxyflavone

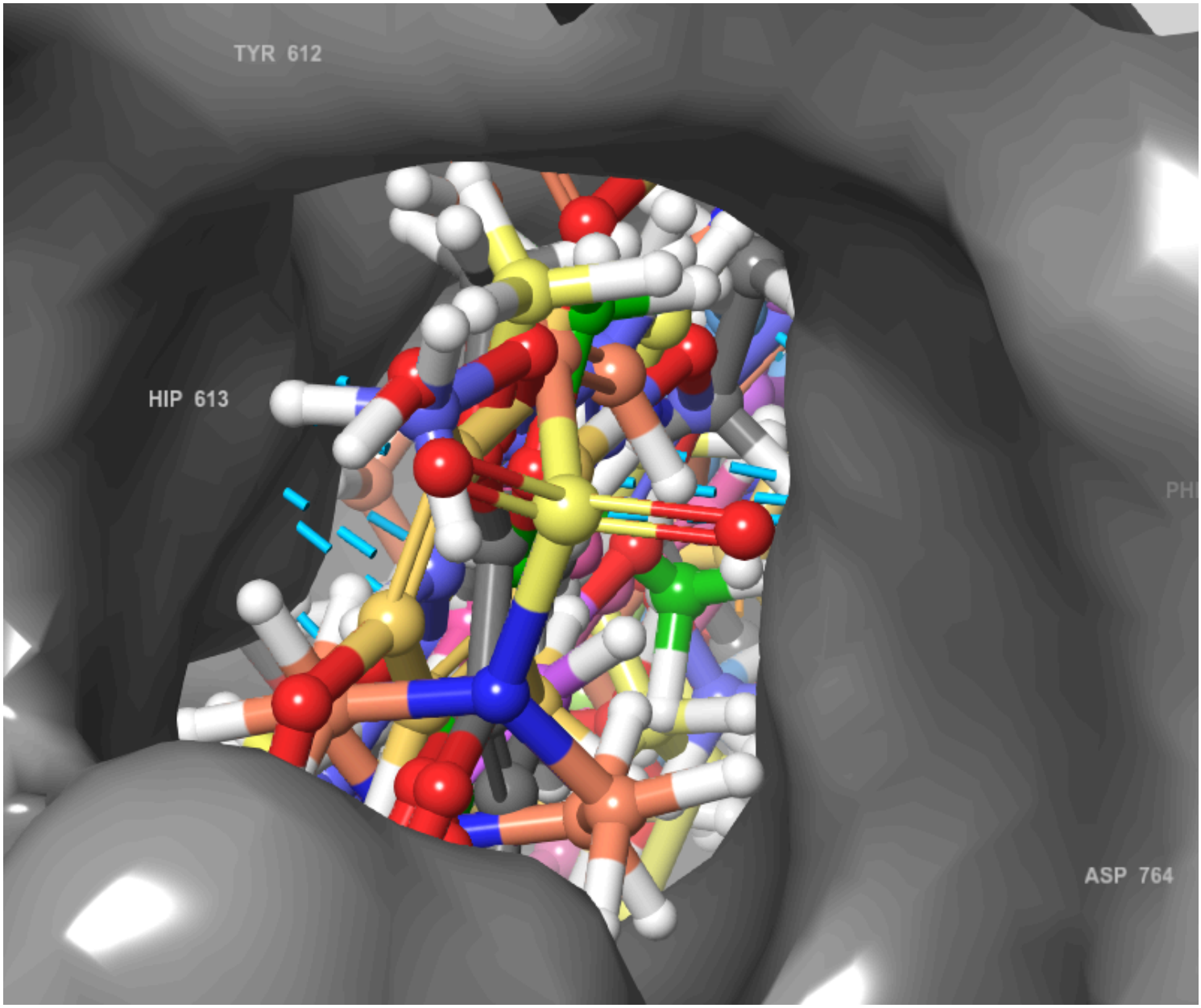


Figure 5

presentation of extra precision binding of all hit compounds to specific binding site

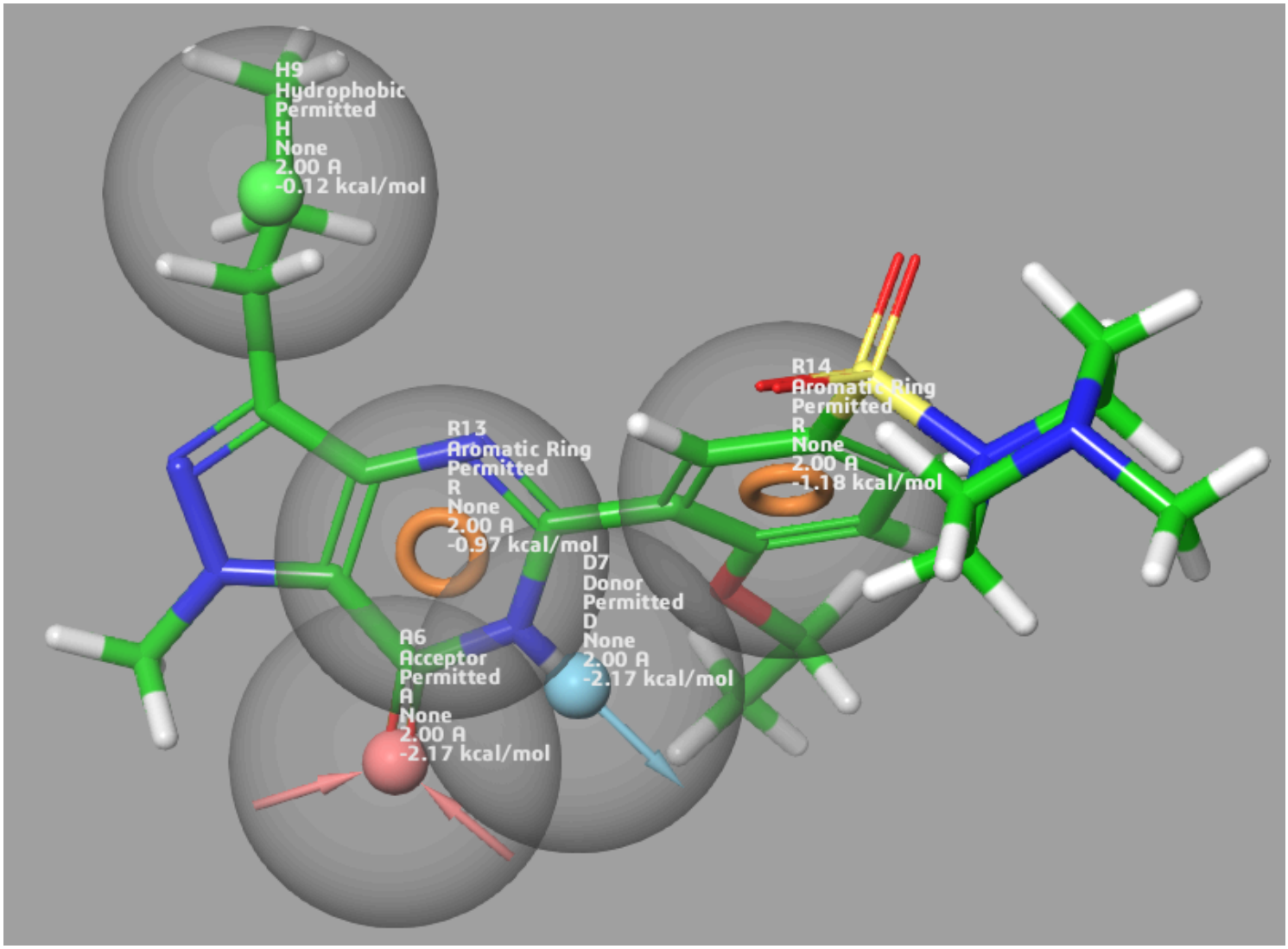


Figure 6

Pharmacophore hypothesis of sildenafil and PDE-5

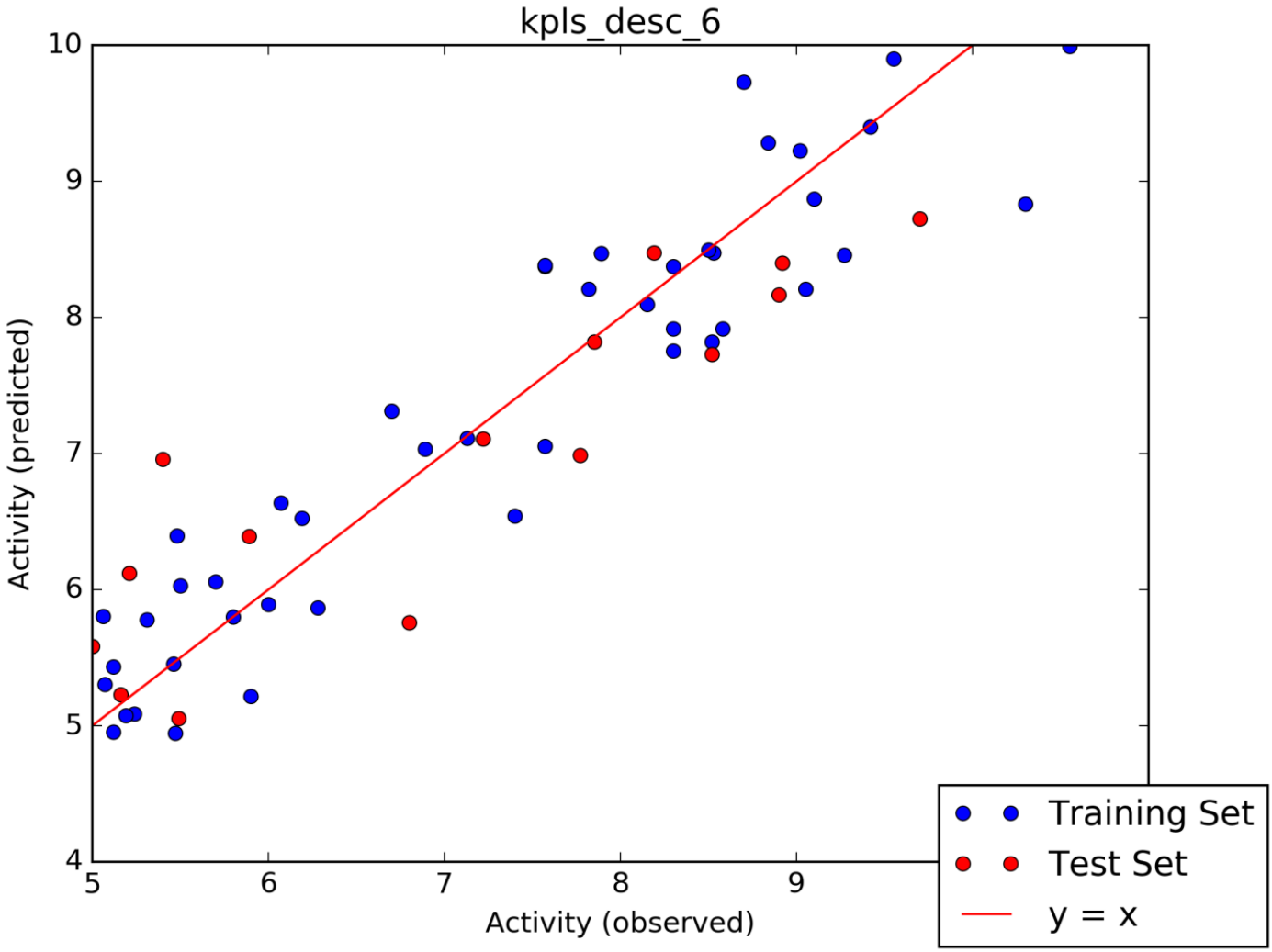
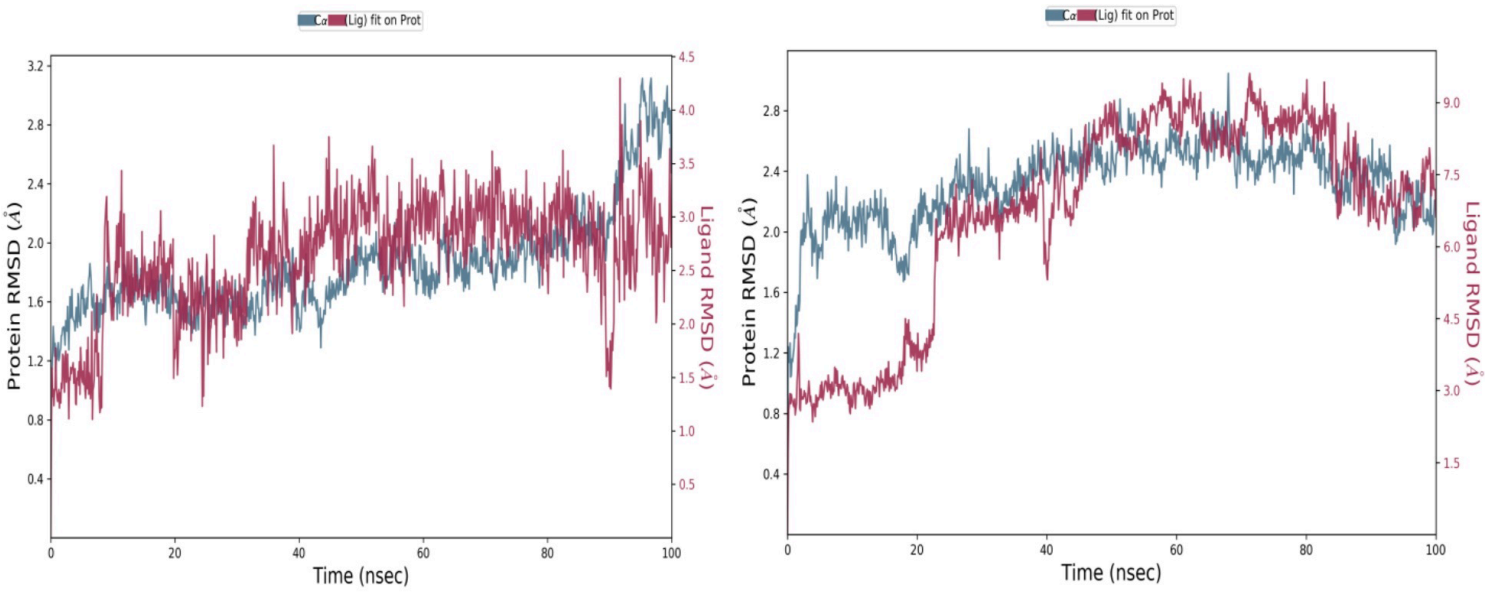


Figure 7

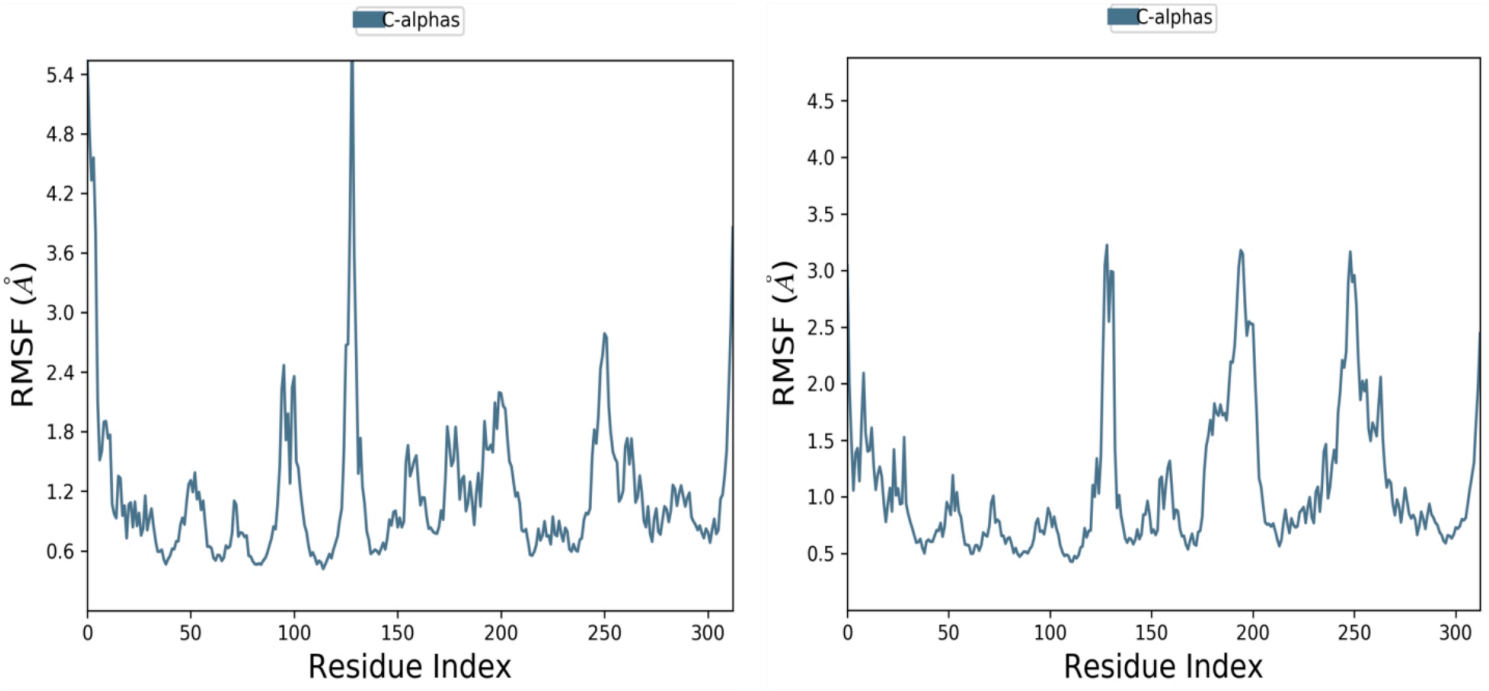
Scatter plot from AutoQSAR modeling



Co-Ligand-PDE-5 Complex Compound 1-PDE-5 Complex

Figure 8

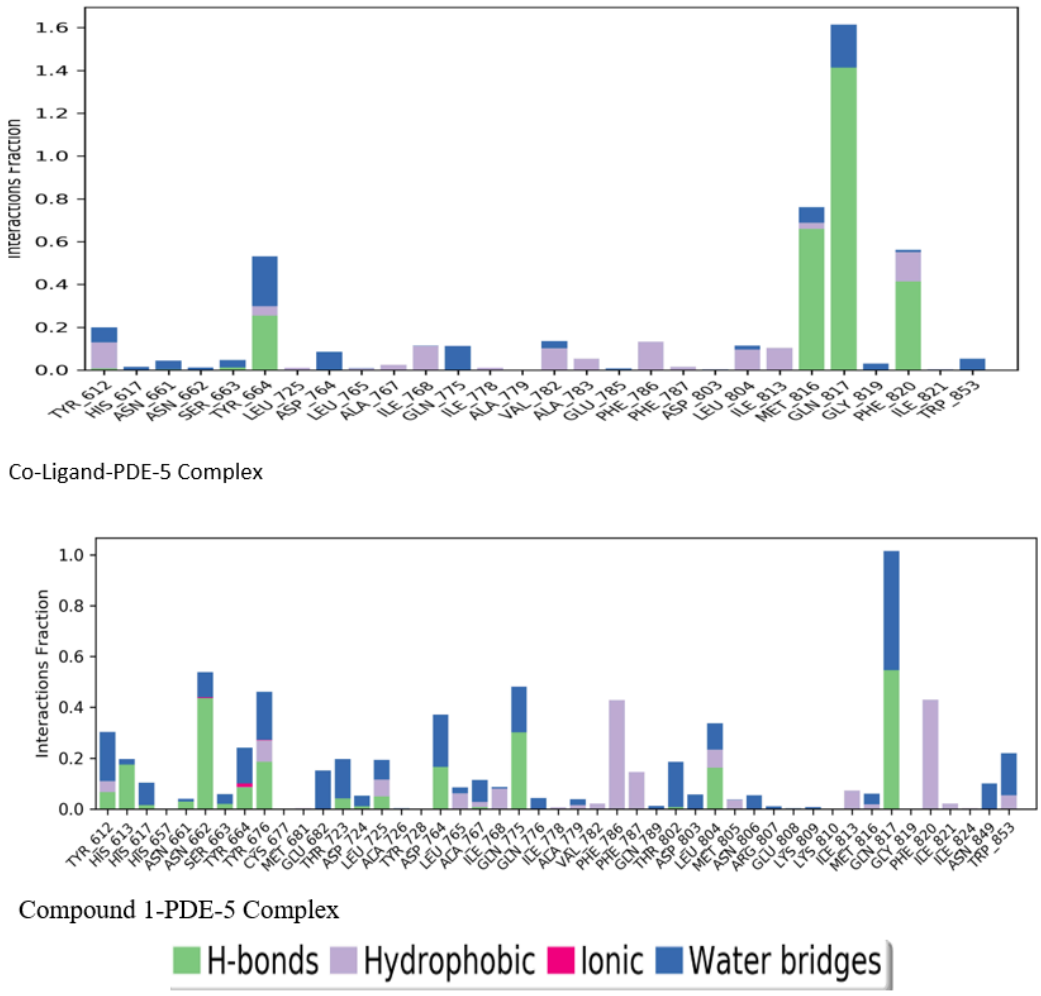
Evaluation of RMSD of protein-ligand complex for 100 ns



Co-Ligand-PDE-5 Complex Compound 1-PDE-5 Complex

Figure 9

Representation of the Root mean square fluctuation (RMSF) of complex over 100 ns simulation



Co-Ligand-PDE-5 Complex

Compound 1-PDE-5 Complex

Figure 10

Complex protein-Ligand interaction mapping

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